C(11A)	0.7510 (4)	0.8070 (4)	1.0359 (3)	0.063 (1)
C(12A)	0.6960 (5)	0.8862 (3)	0.9975 (3)	0.069 (1)
C(13A)	0.5718 (4)	0.8860 (3)	0.9470 (3)	0.057 (1)
C(14A)	0.5180 (3)	0.6976 (2)	0.5832 (2)	0.039 (1)
C(15A)	0.5566 (5)	0.6054 (3)	0.5810 (3)	0.063 (1)
C(16A)	0.6883 (5)	0.5758 (4)	0.5410 (3)	0.078 (1)
C(17A)	0.7760 (4)	0.6388 (4)	0.5048 (3)	0.074 (1)
C(18A)	0.7367 (4)	0.7305 (4)	0.5058 (3)	0.068 (1)
C(19A)	0.6064 (4)	0.7612 (3)	0.5457 (3)	0.054 (1)
Se(1B)	0.3113 (1)	0.4731 (1)	0.1585 (1)	0.063 (1)
Se(2B)	0.2800 (1)	1.0140 (1)	0.3003 (1)	0.053 (1)
S(1B)	0.0761 (1)	0.7409 (1)	0.2516 (1)	0.035 (1)
N(1B)	0.1081 (3)	0.6151 (2)	0.2143 (2)	0.041 (1)
N(2B)	0.3290 (3)	0.6604 (2)	0.2179 (2)	0.036 (1)
N(3B)	0.3183 (3)	0.8221 (2)	0.2525 (2)	0.034 (1)
N(4B)	0.0938 (3)	0.8682 (2)	0.2823 (2)	0.037 (1)
C(1B)	0.2415 (3)	0.5869 (2)	0.1990 (2)	0.039 (1)
C(2B)	0.2580 (3)	0.7411 (2)	0.2402 (2)	0.033 (1)
C(3B)	0.2223 (3)	0.8975 (2)	0.2782 (2)	0.036 (1)
C(4B)	0.4847 (3)	0.6397 (2)	0.2276 (3)	0.048 (1)
C(5B)	0.5443 (4)	0.6893 (3)	0.3082 (3)	0.050 (1)
C(6B)	0.5730 (4)	0.7902 (2)	0.2866 (3)	0.050 (1)
C(7B)	0.4665 (3)	0.8360 (2)	0.2219 (2)	0.043 (1)
C(8B)	−0.0112 (3)	0.5595 (2)	0.2035 (3)	0.044 (1)
C(9B)	−0.0797 (4)	0.5259 (3)	0.2805 (3)	0.067 (1)
C(10B)	−0.1995 (5)	0.4770 (3)	0.2714 (5)	0.095 (2)
C(11B)	−0.2516 (5)	0.4608 (3)	0.1883 (6)	0.101 (2)
C(12B)	−0.1820 (6)	0.4946 (3)	0.1110 (5)	0.093 (2)
C(13B)	−0.0629 (4)	0.5446 (3)	0.1192 (3)	0.066 (1)
C(14B)	−0.0326 (3)	0.9229 (2)	0.3072 (2)	0.037 (1)
C(15B)	−0.0677 (4)	0.9386 (3)	0.3993 (3)	0.050 (1)
C(16B)	−0.1971 (5)	0.9857 (3)	0.4215 (3)	0.065 (1)
C(17B)	−0.2890 (4)	1.0136 (3)	0.3539 (4)	0.062 (1)
C(18B)	−0.2536 (4)	0.9965 (3)	0.2633 (3)	0.063 (1)
C(19B)	−0.1238 (4)	0.9515 (2)	0.2391 (3)	0.049 (1)

Table 2. *Selected geometric parameters (Å, °)*

Se(1A)—C(1A)	1.824 (3)	Se(1B)—C(1B)	1.826 (3)
Se(2A)—C(3A)	1.826 (3)	Se(2B)—C(3B)	1.825 (3)
S(1A)—C(2A)	1.719 (3)	S(1B)—C(2B)	1.712 (3)
S(1A)—N(1A)	1.899 (3)	S(1B)—N(1B)	1.901 (3)
S(1A)—N(4A)	1.910 (3)	S(1B)—N(4B)	1.907 (3)
N(1A)—C(1A)	1.304 (3)	N(1B)—C(1B)	1.309 (4)
N(2A)—C(2A)	1.348 (4)	N(2B)—C(2B)	1.344 (4)
N(2A)—C(1A)	1.419 (4)	N(2B)—C(1B)	1.411 (4)
N(3A)—C(2A)	1.344 (4)	N(3B)—C(2B)	1.340 (4)
N(3A)—C(3A)	1.425 (4)	N(3B)—C(3B)	1.418 (4)
N(4A)—C(3A)	1.302 (4)	N(4B)—C(3B)	1.300 (4)
C(2A)—S(1A)—N(1A)	83.1 (1)	C(2B)—S(1B)—N(1B)	82.9 (1)
C(2A)—S(1A)—N(4A)	83.0 (1)	C(2B)—S(1B)—N(4B)	82.8 (1)
N(1A)—S(1A)—N(4A)	166.1 (1)	N(1B)—S(1B)—N(4B)	165.6 (1)
C(1A)—N(1A)—S(1A)	116.0 (2)	C(1B)—N(1B)—S(1B)	115.9 (2)
C(2A)—N(2A)—C(1A)	114.5 (3)	C(2B)—N(2B)—C(1B)	114.7 (3)
C(2A)—N(3A)—C(3A)	114.8 (3)	C(2B)—N(3B)—C(3B)	115.0 (3)
C(3A)—N(4A)—S(1A)	116.0 (2)	C(3B)—N(4B)—S(1B)	116.1 (2)
C(14A)—N(4A)—S(1A)	117.1 (2)	N(1B)—C(1B)—N(2B)	108.8 (3)
N(1A)—C(1A)—N(2A)	109.0 (3)	N(1B)—C(1B)—Se(1B)	127.9 (2)
N(1A)—C(1A)—Se(1A)	127.3 (2)	N(2B)—C(1B)—Se(1B)	123.3 (2)
N(2A)—C(1A)—Se(1A)	123.7 (2)	N(3B)—C(2B)—N(2B)	125.0 (3)
N(3A)—C(2A)—N(2A)	125.4 (3)	N(3B)—C(2B)—S(1B)	117.4 (2)
N(3A)—C(2A)—S(1A)	117.2 (2)	N(2B)—C(2B)—S(1B)	117.5 (2)
N(2A)—C(2A)—S(1A)	117.3 (2)	N(4B)—C(3B)—N(3B)	108.6 (3)
N(4A)—C(3A)—N(3A)	108.7 (3)	N(4B)—C(3B)—Se(2B)	128.5 (2)
N(4A)—C(3A)—Se(2A)	128.3 (2)	N(3B)—C(3B)—Se(2B)	122.9 (2)
N(3A)—C(3A)—Se(2A)	122.9 (2)		

Data collection and data reduction were carried out using standard Enraf–Nonius routines. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1985) and refined using *SHELXL*93 (Sheldrick, 1993). H atoms were placed in geometrically calculated positions and allowed to refine, riding on the atoms to which they are attached, with a common isotropic displacement parameter. The labelled structure diagram was produced using *ORTEP*II (Johnson, 1976).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HR1038). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.

Billing, D. G., Boeyens, J. C. A., Denner, L., Hellyar, M. D., Lai, L.-L., Matthee, A. J. & Reid, D. H. (1992). *Acta Cryst.* C47, 2564–2567.

Billing, D. G., Ferg, E. E., Lai, L.-L., Levendis, D. C. & Reid, D. H. (1993). *Acta Cryst.* C49, 917–921.

Boessenkool, I. K. & Boeyens, J. C. A. (1980). *J. Cryst. Mol. Struct.* 10, 11–18.

Evans, D. G. & Boeyens, J. C. A. (1989). *Acta Cryst.* B45, 581–590.

Hall, S. R., Flack, H. D. & Stewart, J. M. (1992). Editors. *Xtal3.2 Reference Manual.* Universities of Western Australia, Australia, Geneva, Switzerland, and Maryland, USA.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Lai, L.-L. (1992). PhD thesis, University of the Witwatersrand, Johannesburg, South Africa.

Sheldrick, G. M. (1985). *SHELXS*86. *Crystallographic Computing* 3, edited by G. M. Sheldrick, C. Krüger & R. Goddard, pp. 175–189. Oxford University Press.

Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Three Protected Tetrapeptides

Emma Fenude[a] and Gianluigi Casalone[b]

[a]*Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici, CNR, 07100 Sassari, Italy, and* [b]*Centro del CNR per lo Studio delle Relazioni fra Struttura e Reattività Chimica, Via Golgi 19, 20133 Milano, Italy.*
E-mail: casalone@rs6.csrsrc.mi.cnr.it

Abstract

The structures of three protected tetrapeptides, containing the Boc-Gly-Gly-Phe-*X*-OMe chain, *tert*-butoxycarbonyl-glycy-glycl-phenylalanine-leucine methyl ester dihydrate, Boc-Gly-Gly-L-Phe-D-Leu-OMe, $C_{25}H_{38}$-$N_4O_7.2H_2O$, *tert*-butoxycarbonyl-glycy-glycl-phenylalanine-methionine methyl ester dihydrate, Boc-Gly-Gly-L-Phe-D-Met-OMe, $C_{24}H_{36}N_4O_7S.2H_2O$ and *tert*-butoxycarbonyl-glycy-glycl-phenylalanine-norleucine methyl ester dihydrate, Boc-Gly-Gly-D-Phe-L-Nle-OMe, $C_{25}H_{38}N_4O_7.2H_2O$, are described. The three molecules have the same conformation of the tetrapeptide chain and display the same packing, consisting of couples

of molecules linked head-to-tail by two hydrogen (N—H···O) bonds; other hydrogen bonds, also involving two water molecules of crystallization, link these couples together and give rise to a planar structure.

Comment

Endogenous enkephalin, a linear pentapeptide functioning as a natural analgesic with opiate-like activity, occurs in the brain as H-Tyr-Gly-Gly-Phe-Leu-OH (leucine-enkephalin) and H-Tyr-Gly-Gly-Phe-Met-OH (methionine-enkephalin) in varying proportions, depending upon the species (Hughes, Smith, Kosterlitz, Fothergill, Morgan & Morris, 1975).

From the pharmacological viewpoint, endogenous enkephalin is very similar to morphine. The enkephalin molecule is flexible and capable of adopting various folded or extended conformations; this could explain why it is recognized by both μ- and δ-receptor sites (Schiller, 1984). Some μ- or δ-specific analogues of leucine-enkephalin have been obtained by introduction of conformational constraints (Hansen & Morgan, 1984), but attempts to correlate closely any one of the possible conformations of leucine-enkephalin with that of the rigid morphine molecule have failed hitherto. Different crystal structures have been reported for leucine-enkephalin (Smith & Griffin, 1978; Aubry, Birlirakis, Sakarellos-Daitsiotis, Sakarellos & Marraud, 1988) and for its fragments (Prangé & Pascard, 1979).

This work is part of a more general study on the crystalline conformations of enkephalin, its analogues, fragments and related compounds; here we present the crystal structures of Boc-Gly-Gly-L-Phe-D-Leu-OMe, (I), Boc-Gly-Gly-L-Phe-D-Met-OMe, (II), and Boc-Gly-Gly-D-Phe-L-Nle-OMe, (III). We would have preferred to study compounds of the same chiral series, but the preparation of crystals of these substances suitable for X-ray analysis is not easy, so we were satisfied with the first crystals we obtained. The chiral structure of (II) was confirmed by refining the Flack (1983) parameter, while for (I) and (III) this kind of refinement was not significant and the structure was assigned on the basis of chemical synthesis.

(I) R = -CH₂-CH(CH₃)₂
(II) R = -CH₂-CH₂-S-CH₃
(III) R = -CH₂-CH₂-CH₂-CH₃
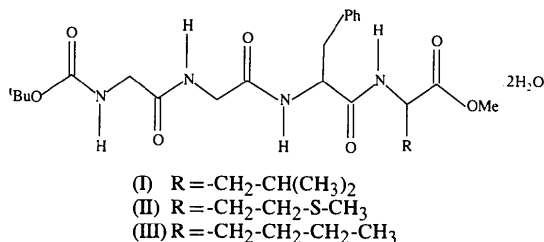
All three compounds have similar structures, with the same space group and cell parameters differing by less than 2%. Fig. 1 shows the three molecules with their atomic numbering schemes. Table 4 reports selected

bond lengths, bond angles and torsion angles. As can be seen, ignoring the sign of the torsion angles and depending on the different chiral series, the equivalent geometrical parameters of the three chains are very close to one another (see Table 4). The tetrapeptide chain presents a conformation all *trans* from N4 to C22 (glycine-glycine group), while the conformation around N2—C22, C22—C21 and N1—C12 is *gauche*, in such a way that the two hydrophobic groups, the benzyl group of phenylalanine and the aliphatic chain of the residue, are nearly coplanar and face each other. Fig. 2 emphasizes the similarities of the conformations of the three molecules. The packing of all these compounds comprises layers of molecules, perpendicular to the c axis; while these layers are linked to each other only by residual forces, the molecules within the layer are bonded by a network of hydrogen bonds, involving the iminic H atoms and those of the two co-crystallized water molecules (see Fig. 3). Table 5 reports the X···O distances of the hydrogen bonds.
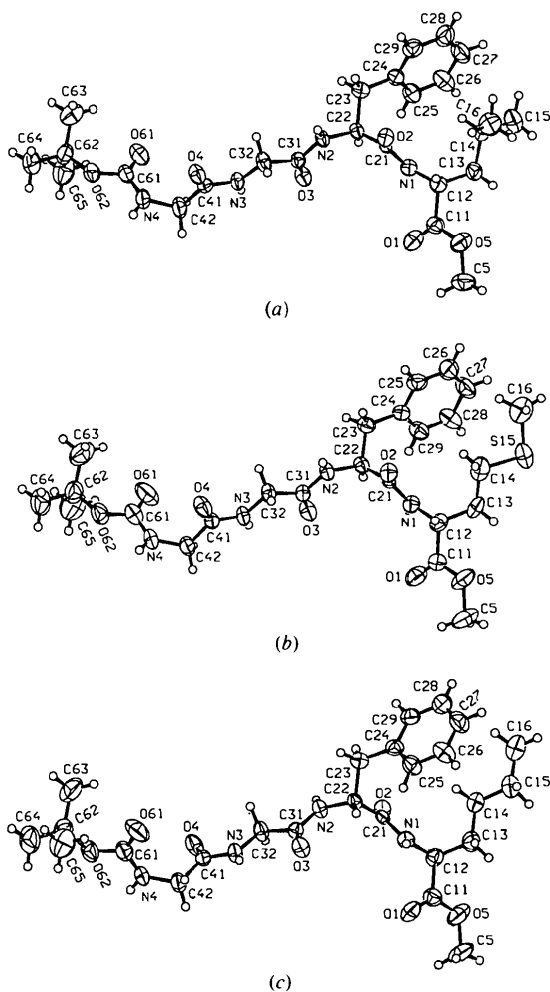

(a)

(b)

(c)

Fig. 1. *ORTEPII* plots of (a) (I), (b) (II) and (c) (III). Ellipsoids are drawn at the 50% probability level and H atoms are not to scale.
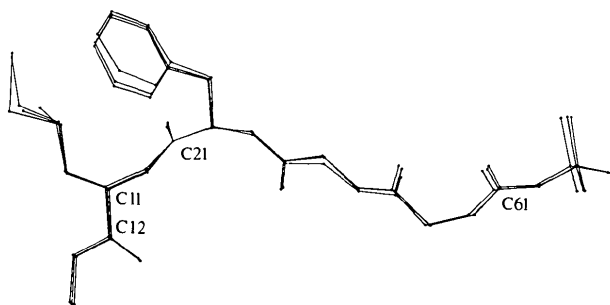
Fig. 2. Schematic projection of the three molecules on the common plane of C11, C12 and C61 with the origin at C21.
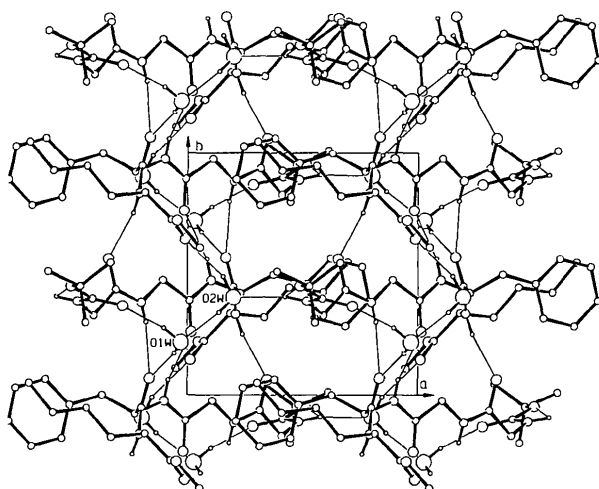

Fig. 3. A layer (1/2 of c axis) of hydrogen-bonded molecules of compound (III). Only H atoms involved in hydrogen bonds (thin lines) are shown. The hydrogen-bonding networks of (I) and (II) are very similar.

Experimental

The synthesis of the tetrapeptides was carried out by conventional methods (Vaughan & Osato, 1952) and the crystals were obtained in all cases from aqueous methanol solutions. The crystals of all three compounds contain two water molecules of crystallization in the asymmetric unit and are stable for a long time at room temperature.

Compound (I)

Crystal data

$C_{25}H_{38}N_4O_7.2H_2O$
$M_r = 542.63$
Orthorhombic
$P2_12_12_1$
$a = 8.826 (1)$ Å
$b = 9.464 (1)$ Å
$c = 35.020 (4)$ Å
$V = 2925.2 (6)$ Å^3
$Z = 4$
$D_x = 1.232$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 36 reflections
$\theta = 2.82–11.85°$
$\mu = 0.094$ mm^{-1}
$T = 293 (2)$ K
Tablet
$0.34 \times 0.30 \times 0.10$ mm
Colourless

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction: none
7424 measured reflections
5163 independent reflections
3643 observed reflections
$[I > 2\sigma(I)]$
$R_{int} = 0.0237$

$\theta_{max} = 25°$
$h = -1 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -41 \rightarrow 41$
3 standard reflections
monitored every 50 reflections
intensity decay: 7.45%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0477$
$wR(F^2) = 0.1071$
$S = 1.055$
5163 reflections
491 parameters
$w = 1/[\sigma^2(F_o^2) + (0.0395P)^2 + 0.2133P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.036$
$\Delta\rho_{max} = 0.200$ e Å^{-3}
$\Delta\rho_{min} = -0.187$ e Å^{-3}

Extinction correction: SHELXL93 (Sheldrick, 1993)
Extinction coefficient: 0.0039 (6)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (I)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
O1	0.0161 (3)	0.3749 (3)	0.12823 (7)	0.0705 (7)
O2	0.1701 (2)	-0.0423 (2)	0.16706 (5)	0.0431 (5)
O3	0.0191 (3)	0.2580 (2)	0.26569 (6)	0.0473 (6)
O4	-0.3525 (2)	-0.0393 (2)	0.32782 (6)	0.0494 (6)
O5	0.0547 (3)	0.3003 (2)	0.06870 (6)	0.0626 (7)
O61	-0.2682 (3)	0.1442 (3)	0.42710 (7)	0.0691 (7)
O62	-0.4941 (3)	0.0543 (2)	0.44758 (5)	0.0520 (5)
N1	0.2203 (3)	0.1897 (3)	0.15750 (7)	0.0376 (6)
N2	0.0980 (3)	0.0476 (2)	0.24269 (7)	0.0351 (6)
N3	-0.2019 (3)	0.1386 (3)	0.30921 (7)	0.0387 (6)
N4	-0.4704 (4)	0.1249 (3)	0.38805 (8)	0.0478 (7)
C11	0.0803 (4)	0.2991 (3)	0.10608 (9)	0.0462 (8)
C12	0.2026 (4)	0.1929 (3)	0.11621 (8)	0.0405 (7)
C13	0.3519 (4)	0.2306 (4)	0.09645 (10)	0.0485 (9)
C14	0.4790 (4)	0.1248 (4)	0.10107 (9)	0.0470 (8)
C15	0.6291 (5)	0.1933 (5)	0.08895 (12)	0.0704 (11)
C16	0.4508 (5)	-0.0091 (4)	0.07891 (13)	0.0728 (12)
C21	0.2039 (3)	0.0762 (3)	0.17937 (8)	0.0308 (6)
C22	0.2288 (3)	0.0990 (3)	0.22181 (8)	0.0330 (7)
C23	0.3708 (4)	0.0207 (3)	0.23589 (9)	0.0420 (7)
C24	0.5176 (3)	0.0570 (3)	0.21599 (8)	0.0393 (7)
C29	0.5597 (4)	0.1962 (4)	0.20944 (9)	0.0478 (8)
C28	0.6953 (5)	0.2289 (5)	0.19174 (11)	0.0637 (10)
C27	0.7894 (5)	0.1229 (6)	0.18014 (11)	0.0701 (11)
C26	0.7517 (4)	-0.0150 (6)	0.18642 (11)	0.0696 (12)
C25	0.6145 (4)	-0.0491 (4)	0.20421 (10)	0.0530 (9)
C31	0.0051 (3)	0.1288 (3)	0.26318 (7)	0.0325 (6)
C32	-0.1174 (4)	0.0489 (3)	0.28389 (9)	0.0428 (8)
C41	-0.3146 (3)	0.0848 (3)	0.33000 (8)	0.0363 (7)
C42	-0.4001 (5)	0.1871 (4)	0.35529 (10)	0.0524 (9)
C5	-0.0476 (5)	0.4068 (5)	0.05437 (13)	0.0739 (12)
C61	-0.3997 (4)	0.1115 (3)	0.42139 (9)	0.0459 (8)
C62	-0.4599 (4)	0.0606 (4)	0.48867 (8)	0.0528 (9)
C63	-0.3202 (6)	-0.0241 (6)	0.49801 (12)	0.0863 (14)
C64	-0.6004 (5)	-0.0054 (5)	0.50578 (11)	0.0738 (12)
C65	-0.4458 (7)	0.2134 (5)	0.50056 (13)	0.0887 (15)
O1W	-0.0189 (4)	0.3083 (4)	0.39413 (9)	0.1062 (11)
O2W	0.2071 (4)	0.1115 (4)	0.36497 (14)	0.1184 (13)

Compound (II)

Crystal data

C$_{24}$H$_{36}$N$_4$O$_7$S.2H$_2$O
M_r = 560.66
Orthorhombic
$P2_12_12_1$
a = 8.919 (2) Å
b = 9.3530 (10) Å
c = 35.408 (4) Å
V = 2953.7 (8) Å^3
Z = 4
D_x = 1.261 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 43
  reflections
θ = 4.7–12.8°
μ = 0.163 mm^{-1}
T = 293 (2) K
Prism
0.34 × 0.20 × 0.18 mm
Colourless

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction:
  none
5889 measured reflections
5202 independent reflections
3944 observed reflections
  [$I > 2\sigma(I)$]
R_{int} = 0.0192

θ_{max} = 25°
h = 0 → 10
k = 0 → 11
l = −42 → 42
3 standard reflections
  monitored every 197
  reflections
  intensity decay: 4.11%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0507
$wR(F^2)$ = 0.1316
S = 1.006
5202 reflections
474 parameters
w = 1/[$\sigma^2(F_o^2)$ + (0.0566P)^2
  + 1.1307P]
  where P = (F_o^2 + 2F_c^2)/3
$(\Delta/\sigma)_{max}$ = 0.058
$\Delta\rho_{max}$ = 0.455 e Å^{-3}
$\Delta\rho_{min}$ = −0.272 e Å^{-3}

Extinction correction:
  SHELXL93 (Sheldrick,
  1993)
Extinction coefficient:
  0.0020 (8)
Atomic scattering factors
  from International Tables
  for Crystallography (1992,
  Vol. C, Tables 4.2.6.8 and
  6.1.1.4)
Absolute configuration:
  Flack (1983) parameter
  = 0.07 (17)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (II)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
S15	0.5968 (2)	0.0886 (2)	0.07234 (5)	0.1253 (7)
O5	0.0488 (3)	0.2810 (3)	0.07083 (8)	0.0775 (9)
O1	0.0119 (3)	0.3584 (3)	0.12932 (8)	0.0696 (8)
O2	0.1694 (3)	−0.0656 (2)	0.17045 (6)	0.0451 (6)
O3	0.0163 (3)	0.2431 (2)	0.26473 (7)	0.0486 (6)
O4	−0.3431 (3)	−0.0604 (2)	0.32839 (7)	0.0536 (6)
O61	−0.2904 (3)	0.1396 (4)	0.41981 (9)	0.0909 (11)
O62	−0.5147 (3)	0.0565 (3)	0.44021 (6)	0.0604 (7)
N1	0.2080 (3)	0.1692 (3)	0.15867 (7)	0.0389 (6)
N2	0.1047 (3)	0.0295 (2)	0.24470 (7)	0.0377 (6)
N3	−0.2021 (3)	0.1210 (3)	0.30762 (8)	0.0401 (6)
N4	−0.4881 (3)	0.1172 (3)	0.38074 (8)	0.0472 (7)
C11	0.0708 (4)	0.2786 (4)	0.10760 (11)	0.0501 (9)
C12	0.1819 (4)	0.1643 (4)	0.11834 (9)	0.0455 (8)
C13	0.3305 (6)	0.1822 (5)	0.09584 (12)	0.0761 (14)
C14	0.4359 (6)	0.0604 (7)	0.10225 (15)	0.090 (2)
C16	0.7049 (8)	−0.0625 (8)	0.0869 (2)	0.111 (2)
C21	0.2007 (3)	0.0564 (3)	0.18124 (8)	0.0334 (7)
C22	0.2312 (3)	0.0840 (3)	0.22305 (9)	0.0357 (7)
C23	0.3733 (4)	0.0075 (4)	0.23653 (10)	0.0445 (8)
C24	0.5176 (4)	0.0470 (3)	0.21654 (9)	0.0406 (7)
C25	0.6232 (4)	−0.0563 (4)	0.20886 (11)	0.0533 (9)
C26	0.7578 (5)	−0.0247 (6)	0.19123 (13)	0.0694 (13)
C27	0.7892 (5)	0.1145 (6)	0.18133 (13)	0.0702 (12)
C28	0.6833 (5)	0.2198 (5)	0.18832 (13)	0.0651 (11)
C29	0.5496 (4)	0.1851 (4)	0.20568 (11)	0.0510 (9)
C31	0.0095 (3)	0.1120 (3)	0.26400 (8)	0.0334 (6)
C32	−0.1056 (4)	0.0286 (3)	0.28618 (10)	0.0410 (8)
C41	−0.3150 (3)	0.0679 (3)	0.32772 (8)	0.0354 (7)
C42	−0.4132 (4)	0.1752 (4)	0.34845 (11)	0.0491 (9)
C5	−0.0545 (7)	0.3905 (7)	0.0567 (2)	0.099 (2)
C61	−0.4210 (4)	0.1085 (4)	0.41400 (11)	0.0545 (9)
C62	−0.4756 (5)	0.0560 (5)	0.48069 (10)	0.0630 (10)
C63	−0.3450 (7)	−0.0408 (7)	0.48729 (15)	0.098 (2)
C64	−0.6159 (7)	−0.0037 (7)	0.49849 (13)	0.090 (2)
C65	−0.4502 (8)	0.2073 (6)	0.4935 (2)	0.104 (2)
O1W	−0.0311 (4)	0.2840 (4)	0.39163 (11)	0.0892 (10)
O2W	0.1945 (4)	0.0977 (4)	0.36033 (12)	0.0915 (11)

Compound (III)

Crystal data

C$_{25}$H$_{38}$N$_4$O$_7$.2H$_2$O
M_r = 542.63
Orthorhombic
$P2_12_12_1$
a = 8.879 (1) Å
b = 9.344 (1) Å
c = 35.674 (4) Å
V = 2959.7 (6) Å^3
Z = 4
D_x = 1.218 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 48
  reflections
θ = 4.5–10.6°
μ = 0.093 mm^{-1}
T = 293 (2) K
Prism
0.50 × 0.48 × 0.28 mm
Colourless

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction:
  none
5913 measured reflections
5225 independent reflections
3647 observed reflections
  [$I > 2\sigma(I)$]
R_{int} = 0.0235

θ_{max} = 25°
h = 0 → 10
k = 0 → 11
l = −42 → 42
3 standard reflections
  monitored every 197
  reflections
  intensity decay: 3.16%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0455
$wR(F^2)$ = 0.1043
S = 1.018
5225 reflections
494 parameters
w = 1/[$\sigma^2(F_o^2)$ + (0.0411P)^2
  + 0.0967P]
  where P = (F_o^2 + 2F_c^2)/3
$(\Delta/\sigma)_{max}$ = 0.391
$\Delta\rho_{max}$ = 0.119 e Å^{-3}
$\Delta\rho_{min}$ = −0.152 e Å^{-3}

Extinction correction:
  SHELXL93 (Sheldrick,
  1993)
Extinction coefficient:
  0.0061 (7)
Atomic scattering factors
  from International Tables
  for Crystallography (1992,
  Vol. C, Tables 4.2.6.8 and
  6.1.1.4)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (III)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O1	0.0116 (3)	0.1449 (3)	0.13012 (7)	0.0723 (7)
O2	0.1652 (2)	0.5684 (2)	0.17018 (5)	0.0450 (5)
O3	0.0170 (2)	0.2613 (2)	0.26518 (5)	0.0505 (5)

O4	−0.3456 (2)	0.5628 (2)	0.32850 (6)	0.0534 (5)
O5	0.0475 (3)	0.2200 (3)	0.07182 (6)	0.0762 (7)
O61	−0.2850 (3)	0.3673 (3)	0.42093 (7)	0.0895 (9)
O62	−0.5114 (2)	0.4508 (2)	0.44125 (5)	0.0614 (6)
N1	0.2100 (3)	0.3342 (2)	0.15882 (6)	0.0396 (5)
N2	0.1015 (3)	0.4741 (2)	0.24430 (6)	0.0388 (6)
N3	−0.2021 (3)	0.3825 (2)	0.30830 (6)	0.0407 (6)
N4	−0.4838 (3)	0.3875 (3)	0.38219 (7)	0.0473 (6)
C11	0.0719 (4)	0.2233 (3)	0.10838 (9)	0.0508 (8)
C12	0.1857 (3)	0.3371 (3)	0.11859 (7)	0.0461 (7)
C13	0.3333 (4)	0.3210 (4)	0.09667 (10)	0.0592 (9)
C14	0.4416 (4)	0.4448 (4)	0.10234 (10)	0.0636 (9)
C15	0.5886 (5)	0.4252 (6)	0.08242 (13)	0.0936 (15)
C16	0.6959 (6)	0.5488 (6)	0.08709 (12)	0.108 (2)
C21	0.1997 (3)	0.4471 (3)	0.18126 (7)	0.0335 (6)
C22	0.2293 (3)	0.4214 (3)	0.22274 (7)	0.0346 (6)
C23	0.3718 (3)	0.4976 (3)	0.23614 (9)	0.0443 (7)
C24	0.5163 (3)	0.4584 (3)	0.21640 (7)	0.0419 (7)
C29	0.6223 (3)	0.5633 (4)	0.20830 (8)	0.0525 (8)
C28	0.7573 (4)	0.5296 (5)	0.19112 (10)	0.0685 (10)
C27	0.7881 (4)	0.3897 (5)	0.18165 (10)	0.0738 (11)
C26	0.6859 (4)	0.2845 (4)	0.18924 (10)	0.0651 (9)
C25	0.5512 (3)	0.3179 (3)	0.20681 (9)	0.0515 (8)
C31	0.0081 (3)	0.3920 (3)	0.26399 (7)	0.0334 (6)
C32	−0.1081 (3)	0.4747 (3)	0.28569 (8)	0.0424 (7)
C41	−0.3144 (3)	0.4352 (3)	0.32843 (7)	0.0360 (6)
C42	−0.4090 (4)	0.3280 (3)	0.35007 (9)	0.0489 (8)
C5	−0.0539 (6)	0.1101 (6)	0.05798 (12)	0.0932 (14)
C61	−0.4158 (4)	0.3982 (3)	0.41520 (9)	0.0545 (8)
C62	−0.4717 (4)	0.4498 (4)	0.48142 (8)	0.0639 (9)
C63	−0.3366 (6)	0.5465 (6)	0.48848 (11)	0.0963 (14)
C64	−0.6122 (5)	0.5104 (6)	0.49943 (11)	0.095 (2)
C65	−0.4465 (6)	0.2984 (5)	0.49415 (14)	0.1004 (15)
O1W	−0.0294 (3)	0.2183 (3)	0.39247 (9)	0.0946 (9)
O2W	0.1985 (3)	0.4040 (3)	0.36100 (10)	0.0967 (9)

Table 4. Selected geometric parameters (Å, °)

	(I)	(II)	(III)
O1—C11	1.199 (4)	1.194 (4)	1.194 (4)
O2—C21	1.237 (3)	1.236 (3)	1.239 (3)
O3—C31	1.231 (3)	1.228 (3)	1.225 (3)
O4—C41	1.224 (3)	1.226 (3)	1.224 (3)
O5—C11	1.329 (4)	1.317 (4)	1.322 (4)
O61—C61	1.218 (4)	1.218 (5)	1.214 (4)
O62—C61	1.352 (4)	1.340 (4)	1.351 (4)
N1—C12	1.454 (4)	1.447 (4)	1.452 (3)
N1—C21	1.328 (3)	1.325 (4)	1.327 (3)
N2—C22	1.450 (4)	1.456 (4)	1.457 (3)
N2—C31	1.333 (3)	1.336 (4)	1.330 (3)
N3—C32	1.436 (4)	1.436 (4)	1.445 (3)
N3—C41	1.333 (4)	1.329 (4)	1.324 (3)
N4—C42	1.431 (4)	1.431 (4)	1.436 (4)
N4—C61	1.330 (4)	1.324 (5)	1.327 (4)
C11—C12	1.516 (5)	1.506 (5)	1.511 (4)
C12—C13	1.531 (4)	1.555 (6)	1.533 (4)
C21—C22	1.518 (4)	1.527 (4)	1.522 (4)
C22—C23	1.537 (4)	1.532 (5)	1.528 (4)
C31—C32	1.506 (4)	1.509 (4)	1.504 (4)
C41—C42	1.513 (4)	1.521 (5)	1.518 (4)
C21—N1—C12	125.3 (3)	124.2 (3)	124.9 (2)
C31—N2—C22	124.6 (2)	124.0 (2)	124.7 (2)
C41—N3—C32	120.0 (3)	120.8 (3)	121.0 (2)
C61—N4—C42	122.7 (3)	121.5 (3)	121.8 (3)
O1—C11—O5	123.4 (3)	124.1 (3)	123.6 (3)
O1—C11—C12	125.6 (3)	124.8 (3)	125.1 (3)
O5—C11—C12	111.0 (3)	111.1 (3)	111.3 (3)
N1—C12—C11	108.8 (3)	109.4 (3)	108.9 (2)
N1—C12—C13	111.2 (3)	111.4 (3)	112.1 (3)
C11—C12—C13	110.6 (2)	110.8 (3)	112.3 (2)
O2—C21—N1	124.0 (3)	124.1 (3)	123.5 (2)
O2—C21—C22	120.3 (2)	119.7 (3)	119.8 (2)
N1—C21—C22	115.7 (2)	116.2 (3)	116.7 (2)
N2—C22—C21	109.3 (2)	108.3 (3)	109.0 (2)
N2—C22—C23	109.0 (2)	108.3 (2)	108.8 (2)
C21—C22—C23	111.3 (2)	111.8 (3)	112.0 (2)
O3—C31—N2	123.3 (3)	123.8 (3)	123.6 (2)
O3—C31—C32	122.4 (3)	122.6 (3)	122.6 (2)
N2—C31—C32	114.3 (2)	113.6 (2)	113.8 (2)
N3—C32—C31	111.9 (2)	111.8 (2)	112.1 (2)
O4—C41—N3	122.4 (3)	122.0 (3)	122.3 (2)
O4—C41—C42	120.9 (3)	121.3 (3)	121.1 (2)
N3—C41—C42	116.6 (3)	116.6 (3)	116.6 (2)
N4—C42—C41	115.0 (3)	113.8 (3)	114.0 (2)
O61—C61—N4	124.6 (3)	124.6 (4)	124.5 (3)
O61—C61—O62	125.3 (3)	124.5 (4)	124.9 (3)
N4—C61—O62	110.2 (3)	110.9 (3)	110.6 (3)
N3—C41—C42—N4	−154.1 (3)	−155.2 (3)	155.4 (3)
C42—C41—N3—C32	−178.7 (3)	−178.2 (3)	178.0 (3)
C41—N3—C32—C31	−179.7 (3)	177.0 (3)	−177.7 (2)
N3—C32—C31—N2	172.6 (3)	177.8 (3)	−176.8 (2)
C32—C31—N2—C22	−176.8 (3)	−176.1 (3)	176.2 (2)
C31—N2—C22—C21	−115.3 (3)	−112.8 (3)	113.6 (3)
N2—C22—C21—N1	126.5 (3)	125.6 (3)	−125.9 (2)
C22—C21—N1—C12	179.8 (3)	−179.7 (3)	180.0 (2)
C21—N1—C12—C11	121.8 (3)	129.7 (3)	−127.5 (3)

Table 5. Hydrogen-bond distances (Å)*

	(I)	(II)	(III)
N1···O4^i	2.864 (3)	2.839 (4)	2.843 (3)
N3···O2^i	3.145 (3)	3.046 (3)	3.051 (3)
N2···O3^{ii}	2.945 (3)	2.907 (3)	2.902 (3)
N4···O2W^{iii}	2.962 (5)	2.927 (5)	2.925 (4)
O1W···O61	2.931 (4)	2.859 (4)	2.850 (4)
O2W···O1W	2.914 (5)	2.883 (5)	2.893 (5)
O1W···O2^i	2.894 (4)	2.887 (4)	2.900 (3)
O2W···O1^{ii}	2.992 (4)	2.921 (4)	2.940 (4)

Symmetry codes for (I) and (II): (i) $-x, \frac{1}{2} + y, \frac{1}{2} - z$; (ii) $-x, -\frac{1}{2} + y, \frac{1}{2} - z$; (iii) $x - 1, y, z$. Symmetry codes for (III): (i) $-x, -\frac{1}{2} + y, \frac{1}{2} - z$; (ii) $-x, \frac{1}{2} + y, \frac{1}{2} - z$; (iii) $x - 1, y, z$.   * X—H···O angles are larger than 147° for (I), 150° for (II) and 159° for (III).

For (I) and (III), H atoms were refined with the geometry restrained (DFIX in SHELXL93; Sheldrick, 1993). For (II), the H atoms bonded to C13 and C14 were constrained to ride on their bonded atoms. The other H atoms were refined with restraints (DFIX in SHELXL93). For all compounds, isotropic B's of methyl groups were constrained to have the same value.

For all compounds, data collection: XSCANS (Siemens, 1994); cell refinement: XSCANS; data reduction: XSCANS. Program(s) used to solve structures: SIR92 (Altomare et al., 1994) for (I); SHELXS86 (Sheldrick, 1990) for (II) and (III). For all compounds, program(s) used to refine structures: SHELXL93 (Sheldrick, 1993); molecular graphics: ORTEPII (Johnson, 1976); software used to prepare material for publication: SHELXL93.

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435-436.

Aubry, A., Birlirakis, N., Sakarellos-Daitsiotis, M., Sakarellos, C. & Marraud, M. (1988). J. Chem. Soc. Chem. Commun. pp. 963-964.

Flack, H. D. (1983). Acta Cryst. A39, 876-881.

Hansen, P. E. & Morgan, B. A. (1984). In The Peptides, Analysis, Synthesis, Biology, Vol. 6, edited by S. Udenfriend & J. Meienhofer. London: Academic Press.

Hughes, J., Smith, T. W., Kosterlitz, H. W., Fothergill, L. A., Morgan, B. A. & Morris, H. R. (1975). *Nature (London)*, **258**, 577–579.

Johnson, C. K. (1976). *ORTEPII*. Report ORNl-5138. Oak Ridge National Laboratory, Tennessee, USA.

Prangé, P. T. & Pascard, C. (1979). *Acta Cryst.* B35, 1812–1819.

Schiller, P. W. (1984). In *The Peptides, Analysis, Synthesis, Biology*, Vol. 6, edited by S. Udenfriend & J. Meienhofer. London: Academic Press.

Sheldrick, G. M. (1990). *SHELXTL/PC User's Manual*. Version 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Siemens (1994). *XSCANS. X-ray Single Crystal Analysis System*. Version 2.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Smith, G. D. & Griffin, J. F. (1978). *Science*, **199**, 1214–1216.

Vaughan, J. R. Jr & Osato, R. L. (1952). *J. Am. Chem. Soc.* **74**, 676–678.

4-tert-Butyloxycarbonyl-6(S)-(hydroxymethyl)-3(S)-(1-methylethyl)piperazin-2-one

THOMAS KOLTER,[a] FRANK RÜBSAM,[a] ATHANASSIOS GIANNIS[a] AND MARTIN NIEGER[b]

[a]*Institut für Organische Chemie und Biochemie der Universität, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany*, and [b]*Institut für Anorganische Chemie der Universität, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany. E-mail: giannis@uni-bonn.de*

Abstract

The six-membered ring of the title ester [IUPAC name: *tert*-butyl 5-(hydroxymethyl)-2-(1-methylethyl)-3-oxo-piperazine-1-carboxylate], $C_{13}H_{24}N_2O_4$, adopts a distorted half-chair configuration with C5 lying out of plane. Hydrogen bonds are formed between the OH group and the protecting carbonyl group, and between NH and the piperazine oxo group.

Comment

Substituted piperazinones are of interest in the development of peptidomimetics, *i.e.* low-molecular weight compounds that can replace peptides in their interaction with receptors (Giannis & Kolter, 1993). The piperazinone ring can serve as a rigid template exposing substituents in a conformation resembling the side chains of a parent peptide in its receptor-bound conformation (Giannis & Kolter, 1993). Little is known about

the three-dimensional structures of these compounds (Michel, Evrard & Norberg, 1987). We report here the structure of the title compound, (I).
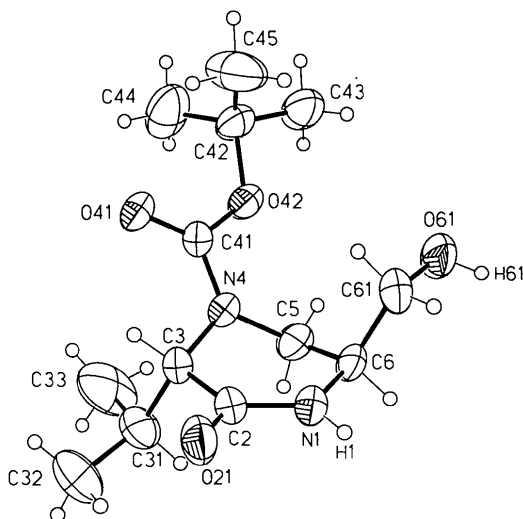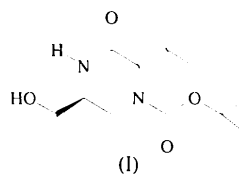

(I)

Fig. 1. Perspective drawing of (I) showing the crystallographic numbering scheme. Non-H atoms are shown with 30% probability ellipsoids.
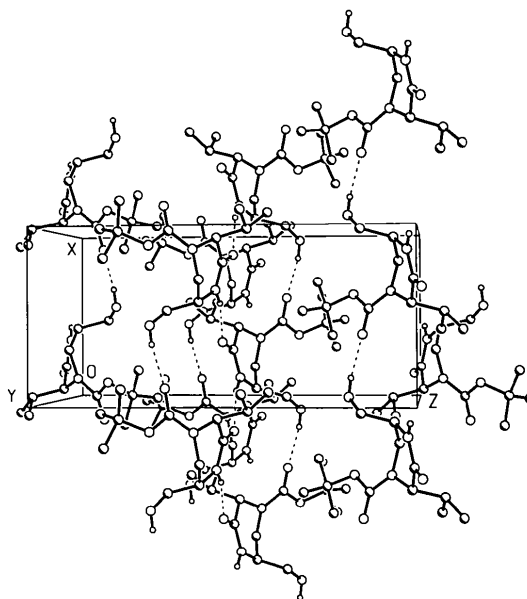

Fig. 2. A view of the unit cell showing intermolecular hydrogen bonding.